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Inhaled Insulin for the Treatment of Diabetes Mellitus

Summary

- **Insulin delivery via inhalation, as an alternative to administration by injection, is under development.**
- **The available evidence comparing subcutaneous (sc) insulin with inhaled insulin for persons with type 1 and 2 diabetes, shows similar glycosylated hemoglobin (HgA1c) levels after three months of treatment.**
- **Clinical trials suggest that insulin delivered by inhalation has a quicker onset of action relative to regular insulin.[1] This means insulin can be taken just prior to a meal rather than the 30 minutes prior to eating required with sc injections of regular insulin.**
- **No changes in pulmonary function were noted in the studies, however data is limited to use for three months. Pulmonary thrombosis has subsequently been reported in one patient out of 1000, using Exubera® and the Inhale Therapeutic Systems device.[2]**

The Technology

Inhalation as a means of systemic delivery of large molecular compounds is not a new concept, however, recent work and technological advances mean it may soon be a reality for the delivery of insulin. For delivery by inhalation, the drug particle must be small enough to get into the lungs (1-3mm),[3] but large enough not to be exhaled.[4] It must also be delivered in a manner that ensures it reaches the lungs rather than being deposited in the mouth and throat. Many devices to deliver insulin deep into lungs are under development.

Inhale Therapeutic Systems, in partnership with the pharmaceutical companies Pfizer and Aventis, is the first company expected to launch a product.[5] Inhale Therapeutic Systems has developed a device that uses compressed air to create a cloud of drug for inhalation. The device, which has no power source, has a clear chamber that holds the drug for inhalation allowing the person to see that all the drug has been inhaled.[6] Pfizer and Aventis are working together to produce the powdered form of insulin, Exubera®, to be used in this device. The drug and device are being tested both in persons with type 1or type 2 diabetes. Although the technology may eliminate the need for daytime injections, patients will still need an injection of long acting insulin late in the day, as Exubera® is only short acting.[4]

Aradigm Corporation is working with Novo Nordisk A/S in the development of the AERx™ Diabetes Management System. This hand-held electronic device uses proprietary technology to create an aerosol from the liquid drug.[4] The drug delivery is dependant on 'proper' breathing and the device has been designed to not release the drug unless the patient's breathing will allow delivery deep into the lungs.[6] This device is being tested in persons with both type 1 and type 2 diabetes. Aerogen Inc. has developed the AeroDose™ system for use by persons with type 2 diabetes.[7]

Pharmaceutical Discovery has developed the Technosphere inhaled insulin. Phase III trials are underway. [8]

Advanced Inhalation Research is about to start human trials of their AIR insulin system.[8]

Epic Therapeutics Inc. (Norwood, MA) is testing their ProMaxx® inhaleable insulin microspheres. Early tests suggest that a metered dose inhaler may deliver the ProMaxx® microspheres deep into the lung.[9]

Regulatory Status

No system has yet been approved in Canada or the United States. Inhale Therapeutic Systems has predicted market availability sometime in 2001.[5]

Patient Group

Diabetes mellitus (DM) is a chronic condition in which the body is unable to properly produce and/or use insulin. Insulin, a hormone produced by the pancreas, helps glucose (both dietary and that produced by the liver) move from the blood stream into cells where it can be used as a source of energy.[7] There are two main types of DM, type 1 and type 2.

In patients with type 1 DM (about 10% of all cases[10]) the pancreas does not produce insulin, usually due to damage or death of the islet cells that normally produce the hormone. Type 1 DM is typically diagnosed during childhood and adolescence. Type 2 DM (about 90% of all cases[10]) generally occurs later in life as a result of insulin resistance and/or relative insulin deficiency.[7]

Over two million Canadians have DM.[10] DM is the seventh leading cause of death in Canada,[11] with an age-standardized mortality of 17.4 per 100,000 in 1997.[12] However, it is estimated that the actual number may be as much as five times higher if deaths with DM as a contribut-ing factor are included.[11] The complications of DM result in morbidity and mortality.[13] DM complications fall into two subdivisions, microvascular and macrovascular.[13] Micro-vascular complications are specific to DM and include: retinopathy, nephropathy, and neuropathy. The clinical consequences can be blindness, kidney failure and amputation.[10] Macro-vascular complications are not unique to DM, and include cardiovascular, cerebrovascular, and peripheral vascular diseases.[10]

Current Treatments

The aim of treatment is to maintain blood glucose at normal or near normal levels (below 7.0mM before meals and below 11mM 1 to 2 hours after meals).[14] Treatment strategies depend on the type of diabetes.

Insulin is indicated for all patients with type 1 DM, as well as patients with type 2 DM who cannot achieve adequate glycemic control by other measures (exercise, diet and/or oral agents).[15] It is estimated that about 40% of people with type 2 DM require insulin.[16] Although exogenous insulin works well to control blood glucose, current administration by injection, either with a syringe, a pen, or a pump is invasive.[17]

In a healthy individual, the pancreas releases insulin, as needed, throughout the day in response to various stimuli. In an effort to mimic physiological function, up to four injections per day are usually required to regulate blood sugar.[10] There are no 'standard' doses of insulin, and dose schedules vary by individual.[15]

The four main preparations of insulin available are: rapid acting, short acting, intermediate acting, and long acting.[18] They differ in their time to onset, time to peak activity, and duration.

Premixed preparations of intermediate and either rapid or short and acting insulins are available.[19]

Dosage and Potential Cost

The bioavailability of inhaled insulin is reported to be 14.7% ± 5.8% relative to sc insulin.[20] In terms of dry powdered insulin, 1mg is approximately equal, in terms of delivery to the circulation, to 3 units of sc insulin.[1]

Price information is not yet available. Some of the devices under development use currently available insulins; others require new formulations (dry powder, microspheres). It is not clear how the cost of these new formulations will compare to currently available formulations. Inhalation will require an initial purchase of the device, however, this can be compared with the costs incurred for the currently available injection methods.

Projected Rate of Diffusion

In the trial done by Inhale Therapeutic Systems, 80% (~56/70) of those with type 1 DM and 92% (47/51) with type 2 DM opted to continue inhaled insulin administration beyond the three month study period.[21,22] If this rate of adoption were achieved and maintained one might expect widespread uptake in a short time frame. However, it has been reported[23] that study participants using sc injection felt less self-conscious about taking insulin while away from home than those taking insulin via inhalation. This may not be the case for all devices.

The maintenance and care of the devices has not been detailed. If very frequent cleaning or care is required enthusiasm may decline.

Concurrent Developments

Efforts are being made to achieve glycemic control with methods that are less invasive and that better mimic physiological conditions. Listed below are some of the new approaches being investigated.

- 'Hexylin' is an oral form of insulin encased in a polymer, which protects it from degradation by the gastrointestinal tract and facilitates its absorption into bloodstream through the gut wall. This formulation has shown predictable effects in clinical studies.[24]
- Once-daily sc injection of insulin glargine (Lantus®) has been approved by the European agency for the evaluation of medicinal products. It is taken at bedtime and has a 24-hour duration of action. The regulated release into circulation provides a peak-less, predictable concentration with a prolonged duration of action. Less nocturnal, but early-morning hypoglycemia has been seen.[25]

- The fungus Pseudomassaria produces an agent (L-783,281) that binds to the insulin receptor, activating the typical insulin biological effect. Discovered by Merck Research Laboratories in Madrid, this agent has been shown to reverse the clinical signs of diabetes in mutant mice. A pill formulation may be feasible if animal studies demonstrate efficacy and safety.[26]

Assessing the Evidence

Eight recent publications of open label, randomized controlled trials of inhaled insulin were identified; six of which are published only in abstract form.[1,21-23,27-30] It is unclear if the eighth publication[23] is a complete report of one of the abstracts,[22] or a unique study. All studies were of three-month duration, however, one abstract only reported 8-week results.[27] All studies report glycemic control through measures of HgA1c. Measures of lung function and occurrence of hypo-glycemia are also reported. Although hypoglycemia was broken down as 'severe' and 'mild or moderate', only two reports[23,28] provided any details on how events were classified.

Four of the eight studies considered treatment of patients with type 1 diabetes.[22,23,29,30] One reported on safety and repro-ducibility, one on patient satisfaction and the other two, which may not be separate studies, reported on efficacy. Patients in the inhaled insulin group took insulin three times daily pre-meal via inhalation, and once daily sc at bedtime. With a total combined sample of between 55 and 91 patients treated with inhaled insulin, both the safety study (n= 20), and the studies on efficacy (n= 35 and 36) reported that inhaled insulin is comparable to sc insulin in terms of glycemic control with no apparent effect on lung function. The patient satisfaction study considered improvements in a quality of life instrument designed by the authors.[31] Results show greater improvements in quality of life in the inhaled insulin group. (The actual scores at baseline and end-of-study may have been more useful).

The remaining four studies considered patients with type 2 DM. In two of the studies, the patients had never received insulin therapy, but were failing glycemic control with oral agents.[27,28] In the other two the patients were already on insulin therapy.[1,21] In both studies of patients failing control with oral agents, those taking inhaled insulin (three times daily, pre-meal) demonstrated a statistically significant ($p < 0.001$) improvement in control of about 2% (±1.17%) compared to the patients who remained on oral agents alone (control group) and showed no improvement (comparison with sc may have been more meaningful). Inhaled insulin three times daily pre-meal with one sc injection at bed-time was as efficacious as sc insulin (as measured by HgA1c), in the other two studies.

As most of these reports are published only in abstract form, there is very limited information on study methodology. Certain important details are not fully reported, such as specific dose, ease of use of the devices, or any training required.

All studies excluded persons with diabetes who smoke, have asthma or have COPD. It is therefore unclear how effective inhalation as a route of insulin administration is for these populations.

Adverse Effects

Of the four studies that assessed lung function at baseline and at study end, none report any change in pulmonary function after treatment with inhaled insulin. Lung function data were reported in one study[23] and values did not differ between the inhaled and the sc groups. Reports of severe, moderate or mild hypoglycemia did not differ between the patients taking insulin via sc injection and those taking insulin via inhalation.

Implementation Issues

The inhalation of insulin requires larger doses than does sc administration as there is more potential for drug to be lost during delivery.

Children may also be more accepting of this means of insulin delivery, but no data are available. Recruitment of children aged 12-17 yr with type 1 DM, to a study on inhaled insulin indicates that studies are planned or may be underway.[32]

It is unclear what dosage adjustments may be needed for patients suffering from respiratory infection.

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